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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/763,982	04/25/2001	Scott L. Diamond	PENN0754	3650

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EXAMINER	
SCHNIZER, RICHARD A	

ART UNIT	PAPER NUMBER
1635	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/763,982	DIAMOND, SCOTT L.	
	Examiner	Art Unit	
	Richard Schnizer, Ph. D	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on *16 October 2003*.

2a)☒ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-12* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-12* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on *25 April 2001* is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a)☐ The translation of the foreign language provisional application has been received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1)☒ Notice of References Cited (PTO-892)
2)☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3)☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____.
4)☐ Interview Summary (PTO-413) Paper No(s). _____.
5)☐ Notice of Informal Patent Application (PTO-152)
6)☐ Other:

DETAILED ACTION

Applicant's amendment submitted 10/16/03 has been entered.

Claim 13 was canceled as requested.

Claims 1-12 remain pending and are under consideration in this Office Action.

Due to the new grounds of rejection set forth below under 35 USC 102 and 103, this Action is NON-FINAL.

The previous indication that claim 8 is allowable is withdrawn in view of the new ground of rejection set forth below.

Rejections Withdrawn

After further consideration, the rejection of claims 12, 4, 5, 7, and 9-12 for lack of enablement is withdrawn. As discussed below, a variety of nonclassical nuclear localization signals was known in the prior art, such that a broad range of embodiments of the claimed invention is enabled. See e.g. rejections under 35 USC 102.

Claim Objections

Claim 3 is objected to because it fails to further limit claim 2 from which it depends.

Double Patenting

A rejection based on double patenting of the "same invention" type finds its support in the language of 35 U.S.C. 101 which states that "whoever invents or discovers any new and useful process ... may obtain a patent therefor ..." (Emphasis added). Thus, the term "same invention," in this context, means an invention drawn to identical subject matter. See *Miller v. Eagle Mfg. Co.*, 151 U.S. 186 (1894); *In re Ockert*, 245 F.2d 467, 114 USPQ 330 (CCPA 1957); and *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970).

A statutory type (35 U.S.C. 101) double patenting rejection can be overcome by canceling or amending the conflicting claims so they are no longer coextensive in scope. The filing of a terminal disclaimer cannot overcome a double patenting rejection based upon 35 U.S.C. 101.

Claim 3 is objected to under 37 CFR 1.75 as being a substantial duplicate of claim 2. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k).

Note that prior to Applicant's last amendment, claim 3 was directed to the composition of claim 2 wherein the nuclear targeting peptide comprises SEQ ID NO:3. After applicant's amendment claim 3 is now identical to claim 2.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-5, 7, and 9-12 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 1-5, and 7 are drawn to the genus of peptides comprising non-classical NLSs that do not interact with importin alpha and importin beta, wherein the peptides do

not contain a classical NLS. Claims 9-12 are drawn to the genus of peptides comprising non-classical NLSs, wherein the peptides do not also contain a classical NLS.

The phrase "signal which does not interact with importin alpha and importin beta" in claims 1-5, and 7 is interpreted as "signal which does not interact with the imprtin alpha subunit of a heterodimer of importin alpha and importin beta". This is interpretation is made in light of the teachings of the prior art that indicate that classical NLSs bind to importin alpha/beta heterodimers through a specific binding site on importin alpha. The importin beta subunit then facilitates transfer of the importin alpha/NLS complex through the nuclear pore. See e.g. Gorlich et al (JOURNAL OF CELL BIOLOGY, (1997 Jul 14) 138 (1) 65-80) paragraph bridging pages 412 and 413. There is no evidence of record that classical NLSs bind to importin beta. So the claimed genus is considered to embrace nonclassical NLSs that do not bind to importin alpha/beta heterodimers, but that do bind to e.g. importin beta monomers or importin beta importin 7 heterodimers such as that taught by Jakel et al (EMBO JOURNAL, (1999 May 4) 18 (9) 2411-23) see abstract.

The term nonclassical nuclear localization signal is interpreted as any NLS identified in the art as nonclassical, and any NLS that does not comprise one or more clusters of basic amino acids that interact with importin alpha. See e.g. Gorlich (1997), paragraph bridging pages 65 and 66, and the instant specification at page 5, lines 2-6. Such sequences would include any sequence lacking a classical NLS but capable of entering the nucleus and binding to a nuclear structure such that, at equilibrium, more of the sequence resided in the nucleus than in the cytoplasm. As examples, see the

abstracts of Grondin et al (J. Biol. Chem. 271(26): 15458-15467, 1996) or Sachdev et al (Mol. Cell. Biol. 18(5): 2524-2534, 1998). Grondin teaches that the zinc finger domain of ZNF74, while not a classical nuclear localization signal, is responsible for the nuclear targeting and localization of ZNF74, and mediates specific binding to RNA in the nuclear matrix. Sachdev teaches that the second ankyrin repeat of IκBα mediates nuclear localization and represents a non-classical NLS, as do ankyrin repeat domains from 53BP2 and GABPβ. See also histone H1, which is not known to interact with importin alpha but instead is known to interact with importin beta and importin 7 monomers and importin beta/importin 7 heterodimers (Jakel 1999).

For a discussion of the written description requirement as applied to genus claims, Applicant is referred to the interim guidelines on written description published December 21, 1999 in the Federal Register, Volume 64 Number 244, pp. 71427-71440 (also available at www.uspto.gov). The following passage is particularly relevant.

> The written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant identifying characteristics, i.e. structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between structure and function, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus.
>
> A "representative number of species" means that the species which are adequately described are representative of the entire genus. Thus, when there is substantial variation within a genus, one must describe a sufficient number of species to reflect the variation within the genus. What constitutes a "representative number" is an inverse function of the skill and knowledge in the art. Satisfactory disclosure of a "representative number" depends on whether one of skill in the art would recognize that applicant was in possession of the necessary common attributes or features of the elements possessed by the members of the genus in view of the species disclosed. In an unpredictable art, adequate written description of a genus which embraces widely variant species cannot be achieved by disclosing only one species within the genus.

The central issue in this analysis is whether Applicant has disclosed a number of species which is representative of the claimed genus. The genus of non-classical NLSs is of indeterminate size, however it is clear that it includes more sequences than the three unrelated species disclosed in the specification (i.e. M9 of hnRNPA1, KNS of hnRNP K, and HNS of HuR), because it must also include sequences that localize to the nucleus by affinity for nuclear structures e.g. zinc finger proteins like ZNF74, κBα, 53BP2, GABPβ, or histone H1 (see above). It is also clear that the claimed genus comprises a high degree of variability inasmuch as the three sequences disclosed by Applicant are not considered to be homologous by those of skill in the art (see Fan et al (PNAS 95: 15293-15298, 1998) at page 15293, column 2, lines 4-6 of paragraph bridging pages 15293 and 15294 who state that HuR (which comprises HNS) "does not however, have any M9-, KNS, or NES-like sequence, suggesting that it may contain a unique shuttling/NES motif."

The specification teaches that the classical NLSs involve peptide sequences of clustered residues that interact with importins alpha and beta, whereas peptides comprising non-classical NLSs do not interact with importins alpha and beta. For example, M9 and HNS enter the nucleus by interacting with transportin, whereas KNS utilizes an alternative importin-independent pathway. Although M9 and HNS utilize the same pathway, they show no homology (see Fan (1998), above) and the specification fails to teach what structural feature these proteins have in common which allows them to utilize the same nuclear import pathway. In fact, the specification fails to establish what structural characteristics define non-classical NLSs generally, instead defining only the structural characteristics of a classical NLS. The specification fails to provide any known or disclosed correlation between structure and function that could be considered to be an adequate description of relevant identifying characteristics of the

genus of non-classical NLSs. For example, the specification fails to teach what structural features are required for other sequences known to have nuclear localization activity such as the zinc finger of ZNF74. In view of the breadth and variability of the genus of non-classical nuclear localization sequences, as well as the fact that these sequences do not all function using the same importin independent pathway, and in view of the failure of the specification to disclose more than three species or to provide any guidance as to any common structural characteristic that is required for the claimed function of importin alpha- and beta-independent nuclear localization, one of skill in the art could not conclude that Applicant was in possession of the claimed broad and highly variant genus of nonclassical nuclear localization signals at the time of the invention.

Response to Arguments

Applicant's arguments filed 13/16/03 have been fully considered but they are not persuasive.

Applicant addresses the written description rejection at pages 7-10 of the response. The essence of Applicant's argument is that the claimed nuclear targeting peptide is any nuclear targeting peptide that does not contain a classical nuclear localization signal, and notes that three species of the genus are discloses at page 8, lines 9-11 (i.e. M9, KNS, and HNS, discussed above in the rejection).

Applicant's arguments are unpersuasive because no evidence or reasoning is presented that shows that the basis of the rejection is incorrect. As established in the rejection, the claimed genus is of indeterminate size but is likely to include alleles and homologs of the disclosed sequences. There is no appreciable homology between the disclosed sequences, so there appears to be substantial variability in the claimed genus. However, the specification provides no guidance as to any correlation between

structure and function such that one of skill in the art could recognize any non-disclosed "non-classical" nuclear import sequence by virtue of its sequence or structure. For these reasons the rejection is maintained.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) and the Intellectual Property and High Technology Technical Amendments Act of 2002 do not apply when the reference is a U.S. patent resulting directly or indirectly from an international application filed before November 29, 2000. Therefore, the prior art date of the reference is determined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

Claims 1-6 are rejected under 35 U.S.C. 102(b) as being anticipated by Michael et al (Cell 82(3): 415-422, 1995).

Michael (1995) teaches a 38 amino acid peptide identical to SEQ ID NO: 3 that functions as a nuclear localization sequence of a fusion partner. See abstract and page 417, column 1, second paragraph to page 418, column 2, first paragraph. Thus Michael anticipates the claims.

Claims 1-5 are rejected under 35 U.S.C. 102(b) as being anticipated by Fan et al (PNAS 95: 15293-15298, 1998), as evidenced by Gallouzi et al (SCIENCE, (2001 Nov 30) 294 (5548) 1895-901).

Fan teaches HNS, a nuclear-cytoplasmic shuttling sequence of HuR which was able to direct nuclear localization of a fusion partner. See e.g. page 15295, column 2, lines 5-13.

Gallouzi teaches that HNS interacts with transportin 2. See abstract.

It is noted that Fan is published after the claimed priority date of this Application (9/1/98). However, a review of the priority document (Provisional Application 60/098,791) indicates that HNS was not contemplated in that application. As a result the priority date for claims 1-5, to the extent that they read on HNS, is 9/1/99, the filing date of PCT/US99/20122. For this reason a rejection under 35 USC 102(b) is required.

Claims 1 and 4 are rejected under 35 U.S.C. 102(b) as being anticipated by Michael et al (EMBO J. 16(12): 3587-3598, 1997).

Michael (1997) teaches the minimal nuclear shuttling domain (KNS) of hnRNP K protein, which was able to direct nuclear localization of a fusion partner. See paragraph bridging columns 1 and 2 on page 3589. Thus Michael anticipates the claims.

Claims 1, 4, and 7 are rejected under 35 U.S.C. 102(a) as being anticipated by Sachdev et al (Mol. Cell. Biol. 18(5): 2524-2534, 1998) as evidenced by GenBank Accession No. 1K5J E (10/10/2001).

Sachdev teaches fusion proteins comprising the nonclassical NLSs of IκBα, 53BP2, or GABPbeta fused to nucleoplasmin core protein. See e.g. page 2528, column 1, first full paragraph, and page 2529, paragraph bridging columns 1 and 2. The fusion proteins were competent for nuclear delivery. See Figs. 6 and 8 on pages 2530 and 2531. As evidenced by the sequence set forth in GenBank Accession No. 1K5J E, nucleoplasmin core protein contains cationic residues and is therefore considered to be a cationic scaffold as required by claim 7.

Thus Sachdev anticipates the claims.

Claims 1, 4, and 7 are rejected under 35 U.S.C. 102(b) as being anticipated by Grondin et al (J. Biol. Chem. 271(26): 15458-15467, 1996)as evidenced by GenBank Accession No. I39311, (12/1/2000).

Grondin teaches that ZNF74 comprises a nonclassical nuclear localization signal that can transport ZNF74 to the nucleus. See entire document, especially abstract. As evidenced by the sequence set forth in GenBank Accession No. I39311, ZNF74

contains cationic residues and is therefore considered to be a cationic scaffold as required by claim 7.

Thus Grondin anticipates the claims.

Claims 1, 4, 7, and 9-12 are rejected under 35 U.S.C. 102(b) as being anticipated by Birnstiel et al (WO92/13570, published 8/20/92) as evidenced by and Jakel et al (EMBO JOURNAL, (1999 May 4) 18 (9) 2411-23) and Gorlich (JOURNAL OF CELL BIOLOGY, (1997 Jul 14) 138 (1) 65-80). .

Claims 1, 4, 7, and 9-12 are rejected under 35 U.S.C. 102(e) as being anticipated by Birnstiel et al (US Patent 5,922,859, issued 7/13/99) as evidenced by Jakel et al (EMBO JOURNAL, (1999 May 4) 18 (9) 2411-23), and Gorlich .

US Patent 5,922,859 is the national stage of the WO 92/13570 patent and is considered to be an accurate translation of that document. As such, these rejections will be discussed by reference to US Patent 5,922,859.

Birnstiel teaches methods for delivering nucleic acids to eukaryotic cells by contacting the cells with compositions comprising a non-classical nuclear localization signal covalently linked to a cationic polypeptide, i.e. histone H1. See paragraph bridging columns 18 and 19, especially column 18, lines 5-12. See also Table 1 at columns 27 and 28. Because histone H1 interacts with importin beta and importin 7 (see Jakel et al (EMBO JOURNAL, (1999 May 4) 18 (9) 2411-23) above) , it is considered to have a NLS. However, because it does not bind importin alpha, the NLS

is not considerd to be a classical NLS because Gorlich teacehs that classical NLSs bind to importin alpha. See paragraph bridging pages 412 and 413.

Thus the Birnstiel references anticipate the claims.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 7 and 9-12 are rejected under 35 U.S.C. 103(a) as being unpatentable over Szoka et al (US Patent 5,661,025, issued 8/26/97) in view of any one of Michael et al (EMBO J. 16(12): 3587-3598, 1997), Michael et al (Cell 82(3): 415-422, 1995), or Fan et al (PNAS 95: 15293-15298, 1998).

Szoka teaches methods of expressing nucleic acids in eukaryotic cells by contacting the cells with compositions comprising a nuclear localization signal covalently linked to polylysine complexed with nucleic acids. See abstract; column 11, lines 50-56; column 16, lines 16-24; and column 17, lines 22-26.

Szoka does not teach a non-classical NLS.

Michael (1997) teaches the minimal nuclear shuttling domain (KNS) of hnRNP K protein, which was able to direct nuclear localization of a fusion partner. See paragraph bridging columns 1 and 2 on page 3589.

Michael (1995) teaches a 38 amino acid peptide identical to SEQ ID NO: 3 of the instant specification which was able to direct nuclear localization of a fusion partner. See abstract and page 417, column 1, second paragraph to page 418, column 2, first paragraph.

Fan teaches HNS, a nuclear-cytoplasmic shuttling sequence of HuR which was able to direct nuclear localization of a fusion partner. See e.g. page 15295, column 2, lines 5-13.

It would have been obvious to one of ordinary skill in the art at the time of the invention to substitute the NLS of any one of Michael (1995), Michael (1997) or Fan (1998) for those disclosed in Szoka. MPEP 2144.06 indicates that when it is recognized in the art that elements of an invention can be substituted, one for the other, while retaining essential function, such elements are art-recognized equivalents. An express suggestion to substitute one equivalent component or process for another is not necessary to render such substitution obvious. In re Fout, 675 F.2d 297, 213 USPQ 532 (CCPA 1982). Furthermore, MPEP 2144.07 indicates that the selection of a known material based on its suitability for its intended use supports the determination of prima facie obviousness. See also Sinclair & Carroll Co. v. Interchemical Corp., 325 U.S. 327, 65 USPQ 297 (1945). In this case, the sequences of Michael (1995), Michael (1997), Fan (1998), and Szoka are all recognized as nuclear localization sequences and

would be reasonably expected to function equivalently inasmuch as they deliver attached molecules to the nucleus. Thus one could have substituted the nonclassical NLSs for the classical NLSs of Szoka with a reasonable expectation of success.

Thus the invention as a whole was prima facie obvious.

Claim 8 is rejected as unpatentable over Szoka et al (US Patent 5,661,025, issued 8/26/97) and Michael et al (Cell 82(3): 415-422, 1995) as applied to claim 7 and 9-12 above, and further in view of Beug (US Patent 5,354,844, issued 10/11/94) and Formoso et al (US Patent 5,260,189, issued 11/9/93).

Szoka and Michael can be combined to render obvious compositions comprising SEQ ID NO:3 covalently conjugated to a cationic peptide scaffold. Szoka teaches that conjugation can be carried out by conventional methods. See e.g. column 17, lines 5-10.

These references do not teach SEQ ID NO:1. SEQ ID NO:1 differs from SEQ ID NO:3 by the addition of the C-terminal sequence GGGC.

Beug teaches conjugation of targeting ligands to cationic peptide scaffolds by formation of disulfide bridges. See e.g. column 5, lines 49-68.

Formoso teaches conjugation of peptides to a carrier protein by disulfide bridge formation, including addition to the peptide of a C-terminal cysteine residue. They cysteine may be spaced from the peptide by the addition of 1-4 glycine residues. See column 8, lines 35-50, and column 12, lines 13-37.

It would have been obvious to one of ordinary skill in the art to add the sequence GGGC to the C-terminus of SEQ ID NO:1 to facilitate disulfide linkage to a scaffold protein. One would have been motivated to do so because addition of the cysteine facilitates conjugation by disulfide formation as taught by both Beug and Formoso. One would have been motivated to provide a glycine spacer because Formoso suggests that this can preserve the function of a conjugated peptide. The selection of a 3 glycine spacer is considered obvious in view of the fact that Formoso suggests a length of 1-4 glycines. The length of the spacer is considered to be a result-effective variable that is routinely optimized by those of ordinary skill.

Thus the invention as a whole was prima facie obvious.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner(s) should be directed to Richard Schnizer, whose telephone number is 703-306-5441 until 1/13/04, and thereafter will be 571-272-0762. The examiner can normally be reached Monday through Friday between the hours of 6:20 AM and 3:50 PM. The examiner is off on alternate Fridays, but is sometimes in the office anyway.

If attempts to reach the examiner by telephone are unsuccessful, the Examiner's supervisor, Andrew Wang, can be reached at 703-306-3217 before 2/22/04, and at 571-272-0811 after 2/22/04. The official central fax number is 703-872-9306 until further notice. Inquiries of a general nature or relating to the status of the application should

be directed to the Patent Analyst Trina Turner whose telephone number is 703-305-3413 prior to 1/14/04, and thereafter will be 571-272-0564.

Richard Schnizer, Ph.D.

DAVE T. NGUYEN
PRIMARY EXAMINER